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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,061	03/05/2002	Francis Y.F. Lee	LD0268 NP	6706

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EXAMINER	
OSTRUP, CLINTON T	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,061	LEE, FRANCIS Y.F.	
	Examiner	Art Unit	
	Clinton Ostrup	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,13-23,26-28,32-35,71,72,74 and 76-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,13-23,26-28,32-35,71,72,74 and 76-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11142003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8, 13-23, 26-28, 32-35, 71-72, 74, and 76-100 are pending in this application.

Priority

Priority to Provision U.S. Application Number 60/275,801, filed March 14, 2001, and Provision U.S. Application Number 60/316,395, filed August 31, 2001, has been acknowledged.

Response to Applicant's Arguments/Amendment

35 USC § 112, First Paragraph-Scope of Enablement

Applicant's amendment and arguments filed November 14, 2003, to the rejection of claims 1-8, 13-23, 26-28, 32-35, 71-72, and 74 under 35 U.S.C. 112, first paragraph, have been fully considered and deemed persuasive. Therefore, the said rejection has been withdrawn.

35 USC § 112, Second Paragraph-Indefiniteness Rejection

Applicant's amendment and arguments filed November 14, 2003, to the rejection of claims 1-8, 13-23, 26-28, 32-35, 71-72, and 74 under 35 U.S.C. 112, first paragraph, have been fully considered and deemed persuasive. Therefore, the said rejection has been withdrawn.

Claim Rejections - 35 USC § 103

Applicant's amendment and arguments filed November 14, 2003, to the rejection of claims 1-8, 13-23, 26-28, 32-35, 71-72, and 74 under 35 U.S.C. 103(a) as being unpatentable over Vite et al., WO 99/02514 and further in view of Saeki et al.,

Mechanism and Possible Biochemical Modulation of Capecitabine (Xeloda), a Newly Generated Oral Fluoropyrimidine, have been fully considered; however, they have not been found convincing. Therefore, the said rejection has been MAINTAINED for claims 1-8, 13-23, 26-28, 32-35, 71-72, and 74 and applied to claims 76-100.

Applicant argues that the Office does not point to any teaching, suggestion, or motivation in the prior art that would lead a skilled artisan to combine Saeki with Vite to arrive at the instantly claimed invention; and therefore, applicant argues that the examiner has used improper hindsight reasoning.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Moreover, each of the references cited are drawn to compositions and methods of using compositions for the treatment of cancer and "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been

individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980).

Vite et al teach, as an example, the specific compound elected by applicant, for the treatment of proliferative diseases including cancer and that the compounds of their invention are useful in combination with other known anti-cancer and cytotoxic agents. The Vite reference teaches methods of treatment wherein the cytotoxic drug combination is chosen for its ability to act on a phase of the cell cycle.

Saeki et al. teaches that capecitabine has been shown to have synergistic or additive effects of capecitabine combined with anti-cancer agents such as, (Taxanes, Mitomycin C or cyclophosphamide), cytokines, growth factors and hormonal agents.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have modified the use of compositions comprising [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]] –7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione to be administered in combination with known anti-cancer and cytotoxic agents as taught by Vite et al. by using the well-known, widely used, orally administered anti-cancer agent, capecitabine, which has been shown to exhibit synergistic or additive effects, when combined with other anti-cancer agents and has a high efficacy rate and low toxicity when used in humans, as taught by Saeki et al. because of the reasonable expectation of obtaining a cancer treating composition and method of using same, which would exhibit synergistic or additive effects, have a high efficacy rate, low toxicity, and be easily administered.

MAINTAINED CLAIM REJECTIONS

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-8, 13-23, 26-28, 32-35, 71-72, 74, and 76-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vite et al., WO 99/02514 and further in view of Saeki et al., Mechanism and Possible Biochemical Modulation of Capecitabine (Xeloda), a Newly Generated Oral Fluoropyrimidine.

Vite et al teach, as an example, the specific compound elected by applicant, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]] –7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione for the treatment of proliferative diseases including cancer. See: page 48, Example 3 and page 8 – page 11, Use and Utility. Vite et al teach that the compounds of this invention are also useful in combination with known anti-cancer and cytotoxic agents and treatments and describe cytotoxic drug combination wherein the second drug chosen acts in a different phase of the cell cycle than the present compounds are especially useful. See: page 10, line 10 – page 11, line 13.

Although the primary reference teaches the specific elected compound elected by applicant, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]] –7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione for the treatment of proliferative diseases

including cancer, the primary reference does not specifically teach the specific elected antiproliferative agent capecitabine.

Saeki et al. teach capecitabine (Xeloda; N-[1-(5-deoxy-b-D-ribofuranosyl)-5-fluoro-1, 2-dihydro-2-oxo-4-pyrimidyl]-n-phenyl carbamate), was generated to decrease the incidence of GI toxicity and to increase the efficacy. The secondary reference teaches that capecitabine was designed as a prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR), which is clinically used for gastric, breast and colorectal cancer patients undergoing single or combination chemotherapy. Saeki et al. teach capecitabine is converted to 5'-DFUR by either human carboxyestelase or cytidine deaminase, which are mainly localized in human liver and 5'-DFUR is converted to the active form of 5-FU by thymidine phosphorylase (dThdPase) in human tumors and the expression of dThdPase is higher in malignant tumors than in noninvolved normal tissues.

Thus, the secondary reference teaches that a high concentration of either 5'-DFUR or 5-FU in malignant tumors may be obtained by oral administration of capecitabine. Saeki et al teach that in vivo studies have shown synergistic or additive effects of capecitabine combined with anti-cancer agents such as, (Taxanes, Mitomycin C or cyclophosphamide), cytokines, growth factors and hormonal agents.

Finally, the secondary reference teaches that capecitabine may be biochemically modulated by those agents in vivo and in the results of an early phase II study on breast cancer patients in Japan, a high efficacy rate and low toxicity has been observed and describes capecitabine as one of the most promising orally administered 5-FU analogs. See: abstract.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have modified the compositions comprising [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]] –7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione in combination with known anti-cancer and cytotoxic agents as taught by Vite et al. by using the well-known, widely used, orally administered anti-cancer agent, capecitabine, which has been shown to exhibit synergistic or additive effects, when combined with other anti-cancer agents and has a high efficacy rate and low toxicity when used in humans, as taught by Saeki et al. It would have been obvious to combine [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]] –7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione with capecitabine in a composition for the treatment of proliferative diseases, such as cancer, because of the reasonable expectation of obtaining a cancer treating composition and method of using same, which would exhibit synergistic or additive effects, have a high efficacy rate, low toxicity, and be easily administered.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clinton Ostrup whose telephone number is (571) 272-0582. The examiner can normally be reached on 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (571) 272-0584. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Clinton Ostrup

Examiner
Art Unit 1614

Frederick Krass
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